

What is claimed is:

1. A transgenic animal whose genome comprises a mammary-specific expression cassette, said expression cassette system comprising:
 - (a) a foreign DNA sequence encoding a mature polypeptide which contains
5 full-coding region or recombinant gene structure;
 - (b) a second DNA sequence which is a secretion signal sequence preceding and operably linked to upstream of (a), said signal sequence encoding a secretional peptide, whereby said mature polypeptide is secreted of high levels into milk by said mammary gland cells;
 - 10 (c) a third DNA sequence which is polyadenylation signal sequence preceding and operably linked to downstream of (a), said polyadenylation signal sequence can be recognized by poly(A)-polymerase for polyadenylation tail editing, whereby said polyadenylation tail acts for stablized the transgene mRNA molecules;
 - (d) a regulatory element of a gene encoding a milk protein of a mammal operably
15 linked to the DNA sequences of (a), (b) and (c) above so as to form a hybrid gene which is expressible in the mammary gland of an adult lactating female of a transgenic animal whose genome comprises said hybrid gene; so that the mature polypeptide is secreted at detectable levels into the milk of said mammal if said mammal is a lactating female.
- 20 2. The transgenic animal whose genome comprises a mammary-specific expression cassette according to claim 1, wherein the regulatory element is selected from the group consisting of alpha-lactalbumin, beta-lactoglobulin, why acidic protein and casein promoters, especially using the bovine alpha-lactalbumin promoter.
- 25 3. The transgenic animal whose genome comprises a mammary-specific

expression cassette according to claim 1, wherein the foreign DNA sequence encoding the mature polypeptide is selected from the group consisting of full-length or B domain-deleted hFVIII polypeptide sequences.

4. The transgenic animal whose genome comprises a mammary-specific expression cassette according to claim 1, wherein the signal peptide is selected from the group consisting of alpha-lactalbumin, aS1-casein signal peptide and other milk protein signal peptides.

5. The transgenic animal whose genome comprises a mammary-specific expression cassette according to claim 1, wherein the signal peptide is an artificial synthetic sequence as SEQ ID: NO. 1 which obtained from the bovine alpha-lactalbumin signal peptide and created a restriction enzyme, HpaI, cloning site in downstream sequence.

6. The transgenic animal whose genome comprises a mammary-specific expression cassette according to claim 1, wherein the signal peptide is an artificial synthetic sequence as SEQ ID: NO. 2 which obtained from the bovine aS1-casein signal peptide and created a restriction enzyme, HpaI, cloning site in downstream sequence.

7. The transgenic animal whose genome comprises a mammary-specific expression cassette according to claim 1, wherein the polyadenylation signal sequence is comprised a bovine growth hormone polyadenylation sequence.

8. The transgenic animal according to claim 1, wherein the mammal is selected from the group consisting of mouse, goat, and pig species.

9. The transgenic animal according to claim 3, wherein said nucleotide sequence encoding the full-length human FVIII polypeptide comprises an intact A1-A2-B-A3-C1-C2 domain sequence, while the intrinsic 19-amino acids signal

peptide was replaced by mammary gland-specific signal peptide sequence.

10. The transgenic animal according to claim 3, wherein said nucleotide sequence encoding the B-domain deleted human FVIII polypeptide comprises a light chain (A3-C1-C2 domain) and a heavy chain (A1-A2 domain) and wherein
5 said light chain and heavy chain are operably linked by a junction.

11. The transgenic animal according to claim 9, wherein said the mammary gland-specific signal peptide sequences are SEQ ID: NO.13 and SEQ ID: NO.14 for 19- residue of alpha-lactalbumin and 15-residue of alpha-S1 casein signal peptides, respectively.

10 12. The transgenic animal according to claim 10, wherein said the B-domain deleted human FVIII polypeptide is SEQ ID: NO.15 for recombinant FVIII construct, such that said created junctional amino acid sequence flanking in Ser-Leu.

13. A method for producing the transgenic animal of claim 1 comprising
15 the steps of:

- a. introducing into a mammalian embryo at least one expression cassette system comprising a DNA sequence encoding a mature polypeptide which intact human FVIII or B domain-deleted human FVIII operatively linked to mammary gland-specific regulatory sequences; and
- 20 b. implanting the embryos into a female of the same species, permitting the embryo to develop to full term and identifying those transgenic mammals which produce in their milk detectable quantities of a mature polypeptide which intact human FVIII or B domain-deleted human FVIII.

14. The method for producing the transgenic animal according to claim 13,
25 wherein 1-50 copies of the mammary gland-specific expression cassette are

introduced into transgenic mammalian genomes.

15. The method for producing the transgenic animal according to claim 13, wherein a plurality of different expression cassettes are introduced and these cassettes express at least two different mature polypeptides which intact human FVIII and B domain-deleted human FVIII.

16. The method of claim 13, wherein the expression level of human FVIII in the milk of said transgenic animals can reach 50 mg/L, and its clotting activity can reach 13-fold than that of normal human plasma.

17. The method of claim 13, wherein the purified human FVIII from the transgenic milk can be applied for supplementary therapy used.